U.S.S.N.: 09/699,003
Filed: October 26, 2000
AMENDMENT

Remarks

Withdrawal of the previous rejections under 35 U.S.C. 112, and objections to the drawing is greatly appreciated.

Rejections under 35 U.S.C. 102(b) or 103

Claims 1-5, 8, 12, 14 and 20 were rejected under 35 U.S.C. 102(b) as anticipated by U.S. Patent No. 4,708,713 to Lentz in combination with Selinsky, et al., Immunology 94(1):88-93 (1998). Claim 14 was previously cancelled.

It is believed this rejection is not appropriate under 35 U.S.C. 102(b), which requires a showing of all of the claimed elements in a single reference. By virtue of the examiner's reference to two different documents, clearly the rejection under 102(b) is inappropriate. The following is a discussion of the art as applied under 35 U.S.C. 103.

Lentz

Lentz describes removal of a large number of proteins using a filter. The only selectivity is by virtue of the molecular weight cutoff of the filter, which is approximately 200,000. ALL proteins in the plasma with the possible exception of some IgM will pass through a filter with a cutoff of 200,000. Therefore the limitations of claims 1-5, 8, 12 and 20 are not met.

Assuming the examiner meant to make a rejection under 35 U.S.C. 103, Selinsky does not make up for the deficiency of Lentz. Lentz teaches away from the selective removal of soluble cytokine receptor molecules. **See col. 6, lines 34 to 46, of Lentz, which states that there are two inhibitors being removed, one, an IgG immunoglobulin type molecule (lines 39-44) and the other which is believed to be a high molecular weight compound (mw between 200,000 and 1,000,000). Neither could possibly be construed to be a soluble cytokine inhibitor such as soluble TNF receptor, which has a significantly lower molecular**

weight. Moreover, Lentz clearly does not know what the inhibitor(s) are, indicating that there are multiple inhibitors. In summary, Lentz teaches one of ordinary skill in the art that (1) the inhibitors are high molecular weight proteins and (2) there are more than one inhibitors involved in immunosuppression of the anti-tumor response, neither of which is a cytokine type molecule.

Selinsky

Selinksky describes an experiment to correlate the levels of soluble tissue necrosis factor receptor ("sTNFR") with tumor burden. This in no way makes obvious the removal of sTNFR to treat tumors or other disorders. The standard under 35 U.S.C. 103 is whether the prior art leads one of ordinary skill in the art to combine the prior art as applicant has done, ***with a reasonable expectation of success.***

The prior art at the time this application was filed in May 1998, was that there were a number of tumor markers that correlated with tumor burden. The most well known include the prostate specific antigen ("PSA") and carcinoembryonic antigen ("CEA"). Studies had been conducted to remove both PSA and CEA, with the hope of decreasing tumor burden. Neither had been effective. Therefore, one skilled in the art would have had no expectation of success that removal of a soluble cytokine receptor such as sTNFR would be effective.

Indeed, this is clearly the opinion shared by the authors of the paper. Enclosed is a copy of the Declaration under 37 C.F.R. 1.132 filed in U.S.S.N. 09/444,144, which subsequently issued as U.S. Patent No. 6,379,708 to Howell, et al. The examiner's attention is drawn to pages 2-3 of the declaration, discussing first the Lentz patent and then the Selinksky paper. As the authors of the Selinsky paper noted:

"It is submitted that, although the statement in Selinsky et al. may cause one of skill in the art to consider how to antagonize or remove sTNFR1 *in situ*, such a statement is merely an invitation to experimentation and opens the door for one of skill in the art to consider a wide range of possible approaches. Indeed, Selinsky et al. provides absolutely no guidance as to how one of skill in the art would go about such a task, but rather generally state that the "therapeutic utility of manipulating sTNFRI levels *in vitro* has been demonstrated" and that "sTNFRI effectively inhibits immune responses *in vivo* and ...its modulation is a legitimate therapeutica avenue." It is submitted that one of skill in the art, when presented with an invitation to manipulate the effects of a soluble protein, would look to a variety of conventional approaches to remove or manipulate the effects of that soluble protein *in vivo*, because such approaches are the most clinically desirable means fo treating a patient."

For the same reasons that the examiner allowed the claims in the Howell patent over the combination of Lentz and Selinsky, so are the claims in this application allowable over Lentz and Selinsky.

Claims 9, 10 and 16-19 were rejected under 35 U.S.C. 103 as obvious over '713 to Lentz in view of U.S. Patent No. 5,523,096 to Okarma, et al. Claim 6 was rejected under 35 U.S.C. 103 as obvious over Lentz and Selinsky in combination with U.S. Patent No. 5,861,483 to Wolpe These rejections are respectfully traversed.

Lentz and Selinsky are discussed above. Neither Okarma nor Wolpe make up for the deficiencies of Lentz and Sclinsky. Okarma does no more than describe immunoaffinity columns for removal of cytokines for treatment of disorders such as septic shock. Wolpe describes the role of some cytokines in mounting an immune response. Wolpe teachcs away

from what is claimd by suggesting one should administer cytokines, not put in soluble receptor molecules.

The prior art fails to teach one of ordinary skill in the art, with a reasonable expectation of success, that one should remove soluble cytokine receptors, my any means, much less an immunoabsorbent column, to treat a disease such as cancer. Lentz teaches that if one removes every protein in the plasma having a molecular weight of about 48,000 (albumin) or larger, tumor reduction will occur. The test under 103 is whether one skilled in the art would be led, by the reference, to combine the references, as applicant has done, with a reasonable expectation of success. There is simply nothing in these references that leads one to that conclusion. The result is simply too unpredictable. Applicant has now conducted numerous trials in humans with a variety of different cancers, and shown that selective removal of soluble cytokines such as sTNFR1 and sTNFR2 does result in an inflammatory response resulting in substantial decrease in tumor volume. This is enhanced by treatment with other types of therapy, including chemotherapy, hyperthermia, and radiation.

The prior art, in combination, says that one should remove ***many proteins, including soluble cytokines*** (which are of a lower molecular weight than albumin) if one wants to treat tumors. Selinsky is merely an invitation to experiment, a discussion of an interesting observation – not a showing that sTNFR could be removed and cause tumor reduction. The prior art provides numerous examples of other tumor burden markers whose removal does not correlate with tumor reduction. The results obtained by applicant are simply too unpredictable.

U.S. Patent No. 6,379,708 to Howell

As the examiner has noted, U.S. Patent No. 6,379,708 to Howell, which is an issued U.S. patent, discloses and claims common subject matter. Howell was issued only after filing of a

declaration under 37 C.F.R. 1.131 (one which the undersigned believes was clearly defective). Applicant requests declaration of an interference to resolve the issue of who is entitled to a patent. Howell's earliest priority date is November 20, 1999. This application claims priority as a continuation of U.S.S.N. 09/316,226 filed May 21, 1999, which is a continuation in part of U.S.S.N. 09/083,307 filed May 22, 1998. Accordingly, Lentz should be declared the senior party.

A proposed count is as follows:

A method of stimulating an immune response in a mammal having a pathological condition comprising:

Contacting the acellular component of blood from a mammal with a binding partner capable of specifically binding to a targeted immune system inhibitor selected from the group consisting of soluble receptors for tumor necrosis factor, interleukin-1 receptor antagonist, soluble receptor for interferon-gamma, soluble receptors for interleukin-1 and soluble receptors for interleukin-6,

Removing the binding partner bound to the targeted immune system inhibitor from the acellular component to produce an altered acellular component having a reduced amount of the targeted immune system inhibitor, and

Administering the altered acellular component, or blood combined with altered acellular component, to the mammal.

This count corresponds to all claims of Howell. Claims 37-44 are further restricted to where the means for binding the targeted immune system inhibitor is an antibody bound to an inert medium to form an absorbent matrix.

This count corresponds to claims 1-4 and 8-10 of the present application.

U.S.S.N.: 09/699,003
Filed: October 26, 2000
AMENDMENT

Allowance of all claims as amended and declaration of an interference is earnestly solicited.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Dated: December 1, 2003
HOLLAND & KNIGHT LLP
One Atlantic Center Suite 2000
1201 West Peachtree Street, N.E.
Atlanta, Georgia 30309-3400
404-817-8473
FAX 404-817-8588

1407516_v1